Drug utilization studies in pregnancy

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SUMMARY

This thesis examines the manner in which drug utilization data obtained from community pharmacies can contribute to a safe and rational use of drugs shortly before and during pregnancy. Three studies were performed with this goal in mind. The first study is based on data relating to 1,948 women obtained from 10 community pharmacies in the north of The Netherlands; it describes the use of prescribed drugs before, during and after pregnancy. In the second study 295 mothers were interviewed a few days after delivery about the medication which they had used during pregnancy. The third study describes the use of ovulation-stimulating drugs in the Dutch population.

In **chapter 1** the background and goal of the studies are given. The history of drug registration in most developed countries is strongly influenced by the thalidomide (Softenon) disaster. This case and other experiences with drugs led drug regulatory authorities to demand a series of extensive animal and clinical/toxicological investigations which should be performed before a drug can be registered. Unfortunately however, these procedures -although they offered an adequate approach to the question of drug safety in general- fail to solve the problem which has led to their introduction, i.e. the safe use of drugs in pregnancy. We realise that knowledge about the safety of drug use related to pregnancy is limited. Data obtained from animal studies are of marginal value for predicting the safety of drugs in human pregnancy. Moreover, for obvious ethical reasons, pregnancy is a contraindication for clinical investigations with new drugs. It thus follows that, in almost every instance, new drugs are necessarily released onto the market without any knowledge on its safety in human pregnancy. In spite of this, it is evident that the large majority of available drugs will, sooner ar later, be used in pregnant women; not uncommonly, risks are taken under uncontrolled conditions. Knowledge about the safety and efficacy of a drug is thus gradually derived from experience in practice. In the WHO report "Drugs in pregnancy and delivery" it was stated that: *"Experiments in human teratogenicity are going on all the time but the results are not being studied."* Therefore a systematic evaluation of drugs used in relation to pregnancy is of high importance.

In **chapter 2** the method of data collection and the characteristics of the drug utilization data from community pharmacies are described. Our data reflect the general prescribing pattern for pregnant Dutch women who have delivered a live-born baby. Various measures to evaluate drug exposure are used. The 'prescription rate', defined as the number of women per 1,000 who received at least one prescription of a given drug, is a fair estimate of prescribing behaviour of the medical profession. While the 'exposure rate', defined as the number of women per 1,000 to whom a given drug is available, is more useful in terms of possible risks for the foetus, because the duration of the prescription is taken into account.

During the course of pregnancy the use of drugs was found to have increased

even when iron preparations and vitamins -the most used drugs- were not taken into account. Most of the women (73%) received one or more iron prescriptions during the course of pregnancy in a low daily dose. The use of antiemetics, antacids, laxatives and treatment for vaginal infections showed a relative increase, whereas the use of cardiovascular, antiinflammatory and central nervous system drugs decreased during pregnancy. At least one percent of the women filled a new prescription for contraceptives in the first trimester of pregnancy. It seems feasible to use pharmacy records as a data base to obtain reliable epidemiological information on drug use during pregnancy. However these pharmacy records have their shortcomings. On the one hand, figures may be underestimated since drugs during hospital stay and over-the-counter drugs are not included. On the other hand, some figures may be overestimated since we do not know to what extent drugs dispensed by the pharmacy are actually consumed.

In **chapter 3** the data obtained directly from the women by interview are presented. In order to validate further the pharmacy data we initiated a complementary study, in which women were interviewed shortly after delivery of their babies about drug use in pregnancy; at the same time we collected the pharmacy records of these same women, after obtaining informed consent. This study is part of the international "Collaborative study on drug use in pregnancy"; we therefore used the international questionnaire. In this questionnaire only open-ended questions were used to collect drug exposure data. From other studies it is known that insufficient recall may occur and that reported drug use varies according to the type of questioning and is directly related to the specificity of the questions asked. We therefore extended this questionnaire with two additional, more specific questions: an indication-oriented and a drug-oriented one. The results of this comparison are discussed. The proportion of self-medication drugs reported increased from 22% after the open-ended to 31% after the more specific questions. Only one out of the nine women who were still using oral contraconceptives in early pregnancy reported this use in the open-ended question. These findings suggest that if drug consumption during pregnancy is evaluated by interview one should not restrict oneself to the open-ended questions, but should include indication-oriented and, as far as desired and possible, drug-oriented questions as well.

The comparison of data from pharmacy records with data obtained from interviews of the mother are presented in **chapter 4**. After excluding the reported self-medication drugs from the interview data, no difference was found between the two sources with respect to the mean number of drugs used per woman. Agreement with respect to the exact number of drugs received per woman was, however, very low (42% with a kappa value of 0.28). Poor agreement was related to a higher percentage of users according to interview data in the case of analgesics, vitamins and non-official drugs whereas in the case of dermatological and respiratory drugs and eye/ear preparations a higher percentage of consumers was found when using pharmacy data. Good agreement was found for the antacids, iron preparations, antibiotics and drugs for vaginal infections. At least one quarter of all prescriptions was not used according to the instructions and 4 out of 10 women admitted not

having followed the instructions adequately. We conclude that the two methods of data collection are clearly complementary to each other.

In **chapter 5 and 6** the prescription records of 1,948 Dutch women were set against the Australian classification of drugs with respect to their known or suspected risk in pregnancy. During pregnancy the use of drugs with proven or anticipated fetal toxicity appears to decrease, indicating that the medical profession is relatively well aware of these potential side effects. In the case of antibiotics the fall in the use of potentially fetal toxic drugs is due to a shift to relatively less fetal toxic drugs whereas the decreased use of analgesics and some antirheumatic drugs is not accompanied by replacement by others. The present study shows that in spite of the generally favourable trends, 168 out of 1000 women received during the course of pregnancy one or more prescriptions from the higher risk categories. When the pattern of changes in use of these drugs was studied in terms of women who stop (s), continue (c) or begin (b) using the drug during pregnancy, the ratios s/(c+b) and s/b were the highest for the drugs belonging to the high risk categories and the lowest for drugs from the low risk categories. The data from this analysis indicate that the prescribing physician is generally aware of the possible risks of drug use during pregnancy. The s/(b+c) and s/b ratios are shown to be a good measure of prescribing behaviour in relation to pregnancy and can be used to compare knowledge of theory with daily practice.

Viewed against the background outlined above, an additional study is presented in **chapter 7**, in which one particular treatment under suspicion of exerting teratogenic effects is analyzed, namely the use of ovulation-stimulating drugs in a representative sample of a population of Dutch women. Several authors have reported a possible association between ovulation induction on the one hand and the occurrence of neural tube defects and neuro-ectodermal tumours on the other hand. This study gives us the opportunity to estimate the number of cases of neural tube defects and the number of neuro-ectodermal tumours attributable to ovulation induction. Clomiphene, the most frequently used ovulation-inducing drug, is seldom used alone. A considerable percentage of the women received at least four different ovulation-inducing and related drugs during the observation period of two years. Thirty percent of the women who used clomiphene were treated for 6 or more cycles. These findings argue for a relative "overuse" of clomiphene. Buserelin, a drug not registered for the indication ovulation induction in The Netherlands but used in in vitro fertilization (IVF) programs, was nevertheless frequently prescribed to these women. This study indicates that, though the potential risks of congenital malformations due to ovulation induction are difficult to assess, they may be considerable; this, and the fact that different ovulation-inducing drugs are used together with clomiphene, emphasizes the need for post-marketing surveillance.

Finally, in the **last chapter** we focused on the basic question posed in the title of this thesis: "Can drug utilization studies contribute to the safe use of drugs in pregnancy?" Our study was a retrospective one, in that the woman was selected for inclusion only after the birth of a live child. The data which can be mobilized in this way prove so informative, and the process of mobilizing them is so cost-effective

that the method can be recommended for a more widespread use. With some simple supplementation this technique might well be used on a prospective and continuous basis, subject to agreement between the individual pharmacist, the individual physician, the midwife and the woman herself. Consent by the woman is needed to allow the pharmacist to be informed of the woman's pregnancy at an early stage. It will provide the opportunity to evaluate prescribing behaviour very closely, and the latter can then be discussed in pharmacotherapeutic consultation between the pharmacist and physician in order to promote safe drug use in pregnancy. In addition, drug utilization data from a series of individual community pharmacies, taken together, create a valuable data base for pharmaco-epidemiological studies in the community. By combining such drug utilization studies with data from registries of congenital abnormalities one will be able to develop the fund of knowledge and the classification of drugs with respect to their risks in pregnancy can be assured to be as accurate as it can reasonably be.

This study has centred largely on the role which pharmacy data can play in studying, monitoring and optimalizing drug use in pregnancy, but in essence the lessons to be derived from it may well prove to be of much broader application. Where high risk groups are concerned, be they pregnant women, children, the eldery, invalids or others with a particular susceptibility to drug injury, there is a need for ever better routines to ensure that data on drug use and drug risk are available, are understood and are properly used to patient's benefit. In that process, essentially a mutual one involving the physician, the pharmacist and the patient, the community pharmacy and the wealth of data which it has at its disposal can play a most important role.